Circulation

ORIGINAL RESEARCH ARTICLE

Spectrum of Cardiac Manifestations in COVID-19

A Systematic Echocardiographic Study

BACKGROUND: Information on the cardiac manifestations of coronavirus disease 2019 (COVID-19) is scarce. We performed a systematic and comprehensive echocardiographic evaluation of consecutive patients hospitalized with COVID-19 infection.

METHODS: One hundred consecutive patients diagnosed with COVID-19 infection underwent complete echocardiographic evaluation within 24 hours of admission and were compared with reference values. Echocardiographic studies included left ventricular (LV) systolic and diastolic function and valve hemodynamics and right ventricular (RV) assessment, as well as lung ultrasound. A second examination was performed in case of clinical deterioration.

RESULTS: Thirty-two patients (32%) had a normal echocardiogram at baseline. The most common cardiac pathology was RV dilatation and dysfunction (observed in 39% of patients), followed by LV diastolic dysfunction (16%) and LV systolic dysfunction (10%). Patients with elevated troponin (20%) or worse clinical condition did not demonstrate any significant difference in LV systolic function compared with patients with normal troponin or better clinical condition, but they had worse RV function. Clinical deterioration occurred in 20% of patients. In these patients, the most common echocardiographic abnormality at follow-up was RV function deterioration (12 patients), followed by LV systolic and diastolic deterioration (in 5 patients). Femoral deep vein thrombosis was diagnosed in 5 of 12 patients with RV failure.

CONCLUSIONS: In COVID-19 infection, LV systolic function is preserved in the majority of patients, but LV diastolic function and RV function are impaired. Elevated troponin and poorer clinical grade are associated with worse RV function. In patients presenting with clinical deterioration at follow-up, acute RV dysfunction, with or without deep vein thrombosis, is more common, but acute LV systolic dysfunction was noted in ≈20%.

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Clinical Perspective

What Is New?

- We report the first systematic echocardiographic evaluation of consecutive patients requiring hospitalization for coronavirus disease 2019 (COVID-19) infection.
- We found that 32% of patients with COVID-19 have normal echocardiography.
- The most frequent abnormality is right ventricular dilation or dysfunction.
- Among patients developing clinical deterioration during follow-up (20% of hospitalized patients), repeat echocardiogram shows further deterioration of the right ventricular parameters, probably related to increased pulmonary resistance. Five of these patients had deep vein thrombosis.

What Are the Clinical Implications?

- Transthoracic echocardiography should be performed only when clinically indicated to minimize the risk of spreading the infection by COVID-19.
- In patients with clinical deterioration, echocardiography helps establish the mechanism of cardiac injury with significant impact on patient management.

The spectrum of pulmonary coronavirus disease 2019 (COVID-19) infection ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death.[1,2] Recent reports[2,3] suggest that cardiac complications not only are common (≈20%–25%) in COVID-19 infection but also are associated with increased mortality. However, in those reports, cardiac complications were defined according to clinical and laboratory parameters (troponin levels), without any systematic cardiac imaging. Transthoracic echocardiography is the mainstay of cardiac imaging, used to diagnose different causes of heart failure and to assist in patient hemodynamic evaluation, risk assessment, and therapy of patients hospitalized in intensive care units.[4,5] However, although the outbreak of COVID-19 infection started months ago, systematic echocardiographic evaluation of COVID-19 patients has not been routinely performed, perhaps because of the logistical problems involved (ie, related to risk of infection spreading). We performed a complete echocardiographic evaluation of consecutive patients with COVID-19 infection requiring hospitalization. We assessed the frequency of cardiac abnormalities. We examined these echocardiographic parameters stratified by troponin levels and clinical condition. Furthermore, patients experiencing clinical deterioration during their hospitalization underwent a repeat complete echocardiographic assessment.

METHODS

We prospectively studied 100 consecutive adult patients (≥18 years of age) admitted between March 21, 2020, and April 16, 2020, to the Tel Aviv Medical Center because of COVID-19 infection. All patients had a diagnosis of COVID-19 infection confirmed by a positive reverse-transcriptase polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2 in a respiratory tract sample. Demographic data, comorbid conditions, medications, physical examination, lung ultrasound, and laboratory findings (including troponin-I levels) were systematically recorded. Patients were risk-stratified according to their COVID-19 Modified Early Warning Score (MEWS) and Sequential Organ Failure Assessment score.[6,7] A summary of MEWS calculation is presented in Table I in the Data Supplement. All patients underwent comprehensive transthoracic echocardiography within 24 hours of admission as part of a predefined step-by-step protocol. Clinical and imaging data were collected prospectively. Patients who then experienced clinical deterioration underwent repeat echocardiographic assessment. Clinical deterioration was defined as either death or respiratory, hemodynamic, or cardiac deterioration. Respiratory deterioration was defined as acute new-onset hypoxemia requiring mechanical ventilation, veno-venous extracorporeal membrane oxygenation, or both. Hemodynamic deterioration was defined as persistent hypotension requiring vasopressors to maintain a mean arterial pressure ≥65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation. Cardiac deterioration was defined as either an increase in serum levels of cardiac troponin-I above the 99th percentile upper reference limit or malignant arrhythmia (defined as rapid ventricular tachycardia lasting >30 seconds, inducing hemodynamic instability or ventricular fibrillation). The ethics committee of the Tel Aviv Medical Center approved the study (Institutional Review Board No. 0196-20-TLV) and voided the requirement of informed consent for the echocardiographic assessment. To evaluate the presence of subtle echocardiographic abnormalities, we compared the echocardiographic characteristics in patients with COVID-19 infection with the reference values previously published.[4,8,9]

The data that support the findings of this study are available from the corresponding author on reasonable request.

Echocardiography

Echocardiography was performed in a standard manner with the same equipment (CX 50, Philips Medical Systems, Bothell, WA) by cardiologists with expertise in echocardiographic recording and interpretation. In accordance to current guidelines,[10] the following measures were undertaken to minimize the risk of infection: (1) All echocardiographic studies were bedside studies performed at the designated COVID-19 intensive care or internal ward units. (2) All echocardiographic examinations were performed with small dedicated scanners because their disinfection is easier than that of larger machines with high-end ultrasound systems. (3) These echocardiographic scanners were set aside in each COVID-19–designated ward to minimize the risk of infection spread. (4) Personal protection at the time of echocardiographic recordings included airborne precautions, made up of N-95 respirator masks, fluid-resistant gowns, 2 sets

of gloves, head covers, eye shields, and shoe covers. (5) Electrocardiographic monitoring during imaging was omitted, and all measurements were performed offline to reduce exposure and contamination.

Left ventricular (LV) diameters, volumes, ejection fraction (LVEF), and mass were measured as recommended.[4] Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling (A wave) velocities, E/A ratio, and deceleration time of early filling velocity. Early diastolic mitral septal and lateral annular velocities (e′) were measured in the apical 4-chamber view.[8] Left atrial volume was calculated with the biplane area-length method at end systole. Forward stroke volume was calculated from the LV outflow tract with subsequent calculation of cardiac output and index.

Right Ventricular Assessment

From 4-chamber views encompassing the entire right ventricle (RV), end-systolic and end-diastolic RV areas and tricuspid annulus were measured. Apart from qualitative grading, RV function was evaluated by tricuspid annular plane systolic excursion, systolic tricuspid lateral annular velocity (RV S′) measured in the apical 4-chamber view, fractional area change, and index of myocardial performance (Tei index).[4,11] Hemodynamic right-sided assessment included the measurement of the pulmonic flow acceleration time (AT) velocity to assess pulmonary vascular resistance.[9]

Lung Ultrasound

We performed lung ultrasonography on all patients with COVID-19 infection using a 6-zone method for each lung, including a scan of the anterior, lateral, and posterior aspects of the thorax. A point scoring system was used for each region and ultrasound pattern: A lines (normal reverberation artifacts of the pleural line that, when accompanied by lung sliding, correspond to normal aeration of the lung) were equal to 0 points; B lines (shining lines vertical to the pleural line, arising from it and reaching the edge of the screen erasing A lines, which represent reverberation artifact through edematous interlobular septa or alveoli) were divided into B1 (separated B lines that correspond to moderate lung aeration loss), equal to 1 point, and B2 (coalescent B lines that correspond to severe lung aeration loss), equal to 2 points. Lung consolidation received 3 points. Thus, a lung ultrasound score of 0 was normal and 36 was the worst.[12]

Statistical Analysis

Continuous normally distributed parameters were presented as mean±SD and compared with the Student *t* test. Normality was assessed with the Shapiro-Wilk test and visual inspection of quantile-quantile plots. Nonnormally distributed data were presented by median and the first and third quartiles and compared with the Wilcoxon rank-sum test. Categorical data were compared between groups with the χ^2 test or Fisher exact test. Normally distributed echocardiographic parameters in consecutive echocardiograms were compared with the paired *t* test. Nonnormally distributed data in consecutive echocardiograms were analyzed by use of the signed Wilcoxon rank-sum test. To compare sample means to known reference values in the population, a 1-sample *t* test was used. Unadjusted correlations between biomarkers and echocardiographic parameters were examined and presented by use of the Spearman rank correlation coefficient for all parameters. To analyze the association of log-transformed biomarkers with LV and RV echocardiographic parameters, we fitted several multivariable regression models with LV and RV echocardiographic parameters as dependent variables and age and MEWS, BNP (B-type natriuretic peptide), C-reactive protein (CRP), and D-dimer as independent variables. Improvement in the predictive value of multivariable linear regression versus univariable models was assessed by a lower root-mean-squared error. All biomarkers were entered into the initial models and selected on the basis of stepwise regression by a backward propagation approach. Cox proportional hazards models for mortality or clinical deterioration as end points allowed the calculation of hazard ratios of baseline echocardiographic parameters. Values of $P<0.05$ were considered to indicate statistical significance. All data were analyzed with the JMP System software version 12.0 (SAS Institute, Inc, Cary, NC). All authors participated in designing the study, collecting and analyzing data, and drafting and revising the manuscript.

RESULTS

Clinical data were collected in 112 consecutive patients hospitalized with COVID-19 infection. A total of 12 patients were excluded because they did not undergo echocardiographic assessment. The reasons for not performing the echocardiogram were as follows: hospital discharge within 24 hours of admission (5 patients), patient refusal (1 patient), and death shortly after hospitalization (6 patients, all >80 years of age and with a "do not resuscitate" status). Thus, the study group included 100 patients who underwent echocardiographic evaluation (66.1±17.3 years of age, 63% male). At the time of baseline echocardiographic evaluation, all patients had dyspnea at rest, stratified to mild disease (oxygen saturation ≥94% at room air) in 61, moderate disease (need for noninvasive oxygen) in 29, and severe disease (need for mechanical ventilation) in 10. Table 1 shows the baseline characteristics and echocardiographic assessments of all patients and stratified by echocardiography results. Comorbidities were present in 72% of patients, with hypertension being the most common, followed by diabetes mellitus, obesity, and coronary artery disease. The most common symptoms on admission were respiratory, followed by only fever, chest pain, and fatigue. Troponin-I, CRP, BNP, and D-dimer were elevated in 20%, 87%, 30%, and 58%, respectively. Bilateral infiltration was the most common chest x-ray manifestation. Pleural effusion and lobar infiltration were rare. Baseline echocardiographic characteristics of patients with COVID-19 infection compared with reference values[4,8,9] are shown in Table II in the Data Supplement. Compared with reference values, patients had smaller LVs and lower LVEF, resulting in

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Table 1. Baseline Characteristics

Parameter	All (n=100)	Normal Echocardiogram (n=32)	Abnormal Echocardiogram (n=68)	*P* Value
Age, mean±SD, y	66.1±17.3	65.9±20	69.8±16	0.56
Male, n (%)	63 (63)	17 (53)	46 (66)	0.25
Cause of admission, %				0.44
Respiratory	64	55	69	
Fever	9	13	7	
Chest pain	9	6	10	
Fatigue	5	10	3	
Neurological	2	0	3	
Gastrointestinal	3	3	3	
Comorbidity	8	13	5	
Body surface area, mean±SD, m^2	1.89±0.3	1.83±0.2	1.9±0.2	0.18
Ischemic heart disease, n (%)	16 (16)	4 (12)	12 (17)	0.48
Congestive heart failure, n (%)	7 (7)	2 (6)	5 (7)	0.82
S/P coronary artery bypass graft, n (%)	5 (5)	1 (3)	4 (6)	0.53
Atrial fibrillation/flutter, n (%)	15 (15)	4 (12)	11 (16)	0.60
Transient ischemic attack/stroke, n (%)	11 (11)	4 (12)	7 (10)	0.76
Peripheral artery disease, n (%)	3 (3)	0 (0)	3 (4)	0.12
Chronic obstructive pulmonary disease, n (%)	4 (4)	3 (10)	1 (1.5)	0.07
Asthma, n (%)	7 (7)	2 (6)	5 (7)	0.82
Chronic kidney disease, n (%)	10 (10)	2 (6)	8 (11)	0.36
Diabetes mellitus, n (%)	29 (29)	7 (22)	22 (32)	0.26
Smoking, n (%)	8 (8)	2 (6)	6 (9)	0.64
Hypertension, n (%)	57 (57)	15 (47)	42 (62)	0.14
Obesity, n (%)	29 (29)	9 (29)	20 (29)	0.99
Malignancy, n (%)	5 (5)	1 (3)	4 (6)	0.53
Aspirin, n (%)	24 (24)	8 (26)	16 (23)	0.76
$P2Y_{12}$ inhibitor, n (%)	5 (5)	2 (6)	3 (4)	0.71
Direct oral anticoagulant, n (%)	13 (13)	3 (9)	10 (15)	0.43
Angiotensin-converting enzyme, n (%)	17 (17)	8 (26)	9 (13)	0.16
Angiotensin receptor blocker, n (%)	17 (17)	4 (13)	13 (19)	0.38
Diuretics, n (%)	18 (18)	4 (13)	14 (20)	0.48
β-Blocker, n (%)	25 (25)	6 (19)	19 (27)	0.23
Systemic corticosteroids, n (%)	2 (2)	1 (3)	1 (1.5)	0.61
Other anti-inflammatories, n (%)	3 (3)	1 (3)	2 (3)	0.99
Hemoglobin, mean±SD, g/dL	13.1±1.9	13.5±1.9	12.9±1.9	0.19
White blood cells, mean±SD, $10^3/\mu L$	7.9±4.2	7.5±2.9	8.1±4.6	0.77
Neutrophils, mean±SD, $10^3/\mu L$	5.9±3.9	5.7±3.0	6.1±4.2	0.69
Lymphocytes, mean±SD, $10^3/\mu L$	1.2±1	1.1±0.7	1.3±1.1	0.58
Platelets, mean±SD, $10^3/\mu L$	210±88	215±87	208±87	0.72
Sodium, mean±SD, mmol/L	136.5±4.7	137.6±4.7	136.0±4.7	0.12
Potassium, mean±SD, mmol/L	4.1±0.5	4.1±0.5	4.1±0.6	0.89
Creatinine, median (IQR), mg/dL	0.9 (0.7–1.2)	0.85 (0.6–1.0)	0.95 (0.7–1.3)	0.04
Blood urea nitrogen, mean±SD, mg/dL	23.2±17.2	22.8±20	23.4±15	0.44
Lactate dehydrogenase, median (IQR), U/L	474 (364–677)	390 (278–605)	493 (373–683)	0.71
Bilirubin, mean±SD, mg/dL	0.57±0.42	0.51±0.22	0.61±0.49	0.77

(*Continued*)

Table 1. Continued

Parameter	All (n=100)	Normal Echocardiogram (n=32)	Abnormal Echocardiogram (n=68)	*P* Value
Aspartate aminotransferase, median (IQR), U/L	37 (26–61)	37 (25–65)	36 (27–61)	0.76
Alanine transaminase, median (IQR), U/L	29 (19–55)	28 (20–61)	31 (18–51)	0.87
Albumin, mean±SD, g/L	38.5±5.2	39.1±5.4	38.3±5.1	0.66
C-reactive protein, mean±SD, mg/L	79.1±67	64.8±73	80.4±63	0.44
C-reactive protein >5 mg/L, n (%)	87 (87)	23 (72)	64 (94)	0.05
Troponin-I, median (IQR), ng/L	11 (5–39)	11 (3–33)	11 (6–46)	0.39
Troponin-I >28 ng/L, n (%)	20 (20)	5 (15)	15 (22)	0.44
BNP, median (IQR), pg/mL	43 (18–144)	31 (18–23)	43 (18–160)	0.44
BNP >80 pg/mL, n (%)	30 (30)	5 (15)	25 (37)	0.01
D-dimer, mean±SD, mg/L	0.8 (0.4–1.7)	0.8 (0.2–0.9)	0.6 (0.3–1.4)	0.67
D-dimer >0.5 mg/L, n (%)	58 (58)	18 (57)	40 (59)	0.82
Fibrinogen, mean±SD, mg/dL	549.3±151	512.1±183	565.0±134	0.24
Ferritin, median (IQR), ng/mL	403 (171–835)	310 (162–626)	525 (193–945)	0.26
Lung crackles, n (%)	26 (26)	8 (27)	18 (28)	0.87
Leg edema, n (%)	5 (5)	0 (0)	5 (8)	0.05
Heart rate, mean±SD, bpm	83±16	80.1±16	83.4±15	0.41
Systolic blood pressure, mean±SD, mm Hg	133±22	122±20	139±21	0.004
Diastolic blood pressure, mean±SD, mm Hg	75±15	76±15	72±14	0.32
O_2 saturation, median (IQR)	95 (89–98)	94.5 (91.2–98)	95 (92–98)	0.74
Temperature, median (IQR), °C	37.1 (36.7–37.7)	37.2 (36.8–37.5)	37.1 (36.6–37.6)	0.38
Lobar infiltration, n (%)	12 (12)	2 (7)	10 (15)	0.27
Bilateral infiltration, n (%)	45 (45)	13 (43)	32 (47)	0.55
Pleural effusion, n (%)	16 (16)	5 (17)	11 (16)	0.94
Hilar congestion, n (%)	8 (8)	2 (7)	6 (9)	0.66
Normal sinus rhythm, n (%)	77 (77)	23 (88)	54 (93)	0.41
Atrial fibrillation/flutter, n (%)	6 (6)	3 (11)	3 (5)	0.34
Right bundle-branch block, n (%)	5 (5)	2 (8)	3 (5)	0.69
Left bundle-branch block, n (%)	2 (2)	0 (0)	2 (3)	0.21
ST-segment elevation, n (%)	2 (2)	0 (0)	2 (3)	0.21
ST-segment depression, n (%)	4 (4)	0 (0)	4 (7)	0.07
T-wave inversion, n (%)	10 (10)	3 (11)	7 (12)	0.88
Long QT, n (%)	6 (6)	1 (4)	5 (9)	0.38
QTc, mean±SD, ms	416.3±54	421.7±27	413.8±63	0.84
Sequential Organ Failure Assessment score, median (IQR)	1 (0–3)	1 (0–4)	1 (0–3)	0.72
MEWS, median [IQR]	4 (2–7)	4.5 (2–8)	4 (3–7)	0.63
MEWS 3 grades, n (%)				0.78
Low	53 (53)	16 (50)	37 (54)	
Medium	19 (19)	6 (19)	13 (19)	
High	28 (28)	10 (31)	18 (27)	
Lung ultrasound score, median (IQR)	15 (7–21)	16 (6–22)	15 (7–20)	0.92

BNP indicates B-type natriuretic peptide; CRP, C-reactive protein; IQR, interquartile range; and MEWS, Modified Early Warning Score.

lower stroke volume. Nevertheless, 90% of patients had normal LVEF. Low LVEF caused by ischemic heart disease was known in 2 of the 10 patients with low LVEF. Evaluation of indexes of LV filling pressure showed enlarged left atrial volume and increased average E/e′ ratio compared with reference values. Nevertheless, most patients (80%) did not have clearly elevated LV filling pressure (E/e′≥14). On the other hand, RV was enlarged in ≈40% of patients. In terms of indexes of RV function, pulmonary AT was shorter and RV S′ and

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RV fractional area change were lower than reference values, but tricuspid annular plane systolic excursion and Tei index were in the normal range in the majority of patients.

Cardiac Disease Detected by Echocardiography

The most common echocardiographic pattern among patients with COVID-19 infection was RV dilatation with or without dysfunction (39%), followed by LV diastolic dysfunction (16%), LV systolic dysfunction (10%), and valvular heart disease (3 patients: 1 with severe organic mitral regurgitation and 2 with moderate aortic regurgitation). The remaining 32 patients (32%) had a normal echocardiogram (Figure 1). Baseline characteristics and echocardiographic assessments in patients with normal baseline echocardiogram versus abnormal echocardiogram are shown in Table 1. Most clinical characteristics were similar between these groups except for higher creatinine, increased prevalence of elevated BNP and CRP, higher systolic blood pressure, and more peripheral edema in patients with an abnormal echocardiogram.

Subgroup Analyses

Clinical Severity Grade and Echocardiography

We assessed all LV and RV parameters in patients with COVID-19 infection stratified by clinical presentation at baseline echocardiogram. Patients with worse clinical grade had shorter pulmonary AT, suggesting increased RV afterload (Table 2). Of note, there were no significant differences in LV systolic or diastolic function between the patients with worsening clinical grades.

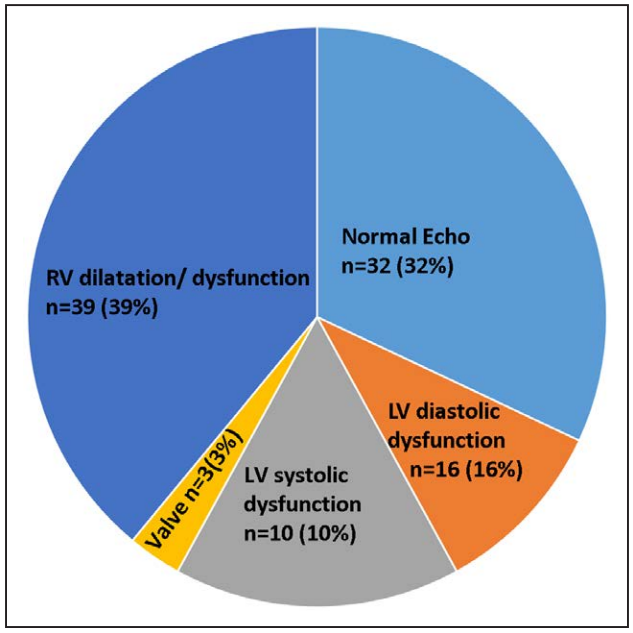

Figure 1. Patterns of cardiac disease in hospitalized patients with coronavirus disease 2019 (COVID-19).
LV indicates left ventricular; and RV, right ventricular.

Pulmonary AT

The most common echocardiographic pattern among patients with COVID-19 infection was RV dilatation related to elevated pulmonary vascular resistance. We assessed all clinical characteristics, including comorbidities, stratified by AT tertiles and present them in Table III in the Data Supplement. Patients with shorter AT (suggesting increased pulmonary vascular resistance) were older, had more comorbidities, and had worse lung disease (based on chest x-ray, lung ultrasound, and lower oxygen saturation). They also had higher levels of biomarkers of adverse prognosis (D-dimer, BNP, troponin-I, and CRP).

Biomarker Levels

Similar to previous reports,[3] 20% of patients with COVID-19 infection had troponin levels above the 99th percentile at presentation. Patients with elevated troponin levels were older and had higher BNP levels and MEWS and Sequential Organ Failure Assessment scores but were otherwise similar to patients with nonincreased troponin levels. All LV linear dimensions and parameters of radial LV systolic function were similar between patients with and without troponin elevation (Table IV in the Data Supplement). However, patients with high troponin levels had a significantly elevated average E/e′ ratio, suggesting that patients with elevated troponin have worse LV diastolic function and higher left atrial pressure. Indexes of RV hemodynamics and function were poorer in patients with elevated troponin. Pulmonary AT was shorter, RV fractional area change was worse, and RV S′ and tricuspid annular plane systolic excursion were lower, suggesting inefficient RV function secondary to increased afterload. Troponin was negatively associated with stroke volume, AT, tricuspid annular plane systolic excursion, and RV fractional area change and positively associated with E-wave velocity, left atrial volume, E/e′ ratio, and Tei index in unadjusted analyses. Spearman correlation analyses with the correlations coefficients and *P* values between all biomarkers and LV and RV parameters are shown in Table V in the Data Supplement. The addition of age, MEWS, D-dimer, CRP, and BNP improved the predictive value of all the models ($P<0.0001$ for all models), but BNP removed troponin from all the models with the exception of RV fractional area change.

Predictors of Outcome

We performed analyses on the echocardiographic and clinical predictors of clinical deterioration or death alone. The only baseline clinical parameters associated with clinical deterioration during hospitalization were obesity (2.6 [hazard ratio (HR), 1.04–6.9]; $P=0.04$), lower platelet count (0.99 [HR, 0.98–0.99]; $P=0.005$), lower O_2

Table 2. Patients Stratified by Clinical Presentation at Baseline Echocardiogram

Variables	Clinical Grade*			*P* Value
	Grade 1(n=61)	Grade 2(n=29)	Grade 3(n=10)	
Age, mean±SD, y	63.2±17	71.3±13	69.4±21	0.07
Male, n (%)	35 (57)	21 (72)	6 (60)	0.26
MEWS, mean±SD	3.0±2	7.9±3	11.0±4	<0.0001
Acuity score (COVID-19 MEWS), (%)				<0.0001
Low	75	14	0	
Medium	18	21	10	
High	7	65	90	
Troponin-I, mean±SD, ng/L	20.8±50	34.3±53	941±2138	0.0006
Positive end-expiratory pressure, mean±SD, cm H_2O	0±0	0±0	11.1±3.2	<0.0001
Fraction of inspired O_2, mean±SD, %	22±4	49±31	70±26	<0.0001
O_2 saturation, mean±SD, %	95.9±3	93.0±4	93.6±4	0.03
Systolic blood pressure, mean±SD, mm Hg	135±22	133±21	129±21	0.79
Diastolic blood pressure, mean±SD, mm Hg	75±14	73±16	72±24	0.74
Vasopressor requirement, n (%)	0 (0)	0 (0)	3 (30)	0.0007
LV assessment				
EF, %	58.2±4	58.2±5	56.0±5	0.33
LV S', cm/s	7.8±3	7.0±2	6.5±2	0.75
LVEDD, mm	42.3±6	45.1±7	41.7±4	0.21
LVESD, mm	26.8±5	29.2±6	27.8±5	0.22
Heart rate, bpm	75.8±14	81.2±19	93.7±25	0.01
Stroke volume, mL	59.9±16	61.3±22	46.8±17	0.10
Cardiac output, L/min	4.6±1.4	4.8±2.0	4.0±1.4	0.45
LA volume, mL	55.7±24	59.6±26	60.6±30	0.65
E wave, m/s	0.66±0.26	0.64±0.18	0.55±0.18	0.42
A wave, m/s	0.64±0.26	0.62±0.14	0.67±0.18	0.75
E/A	1.12±0.4	1.08±0.7	0.77±0.1	0.15
e' Septal, cm/s	6.9±2	5.9±2	5.9±2	0.15
e' Lateral, cm/s	8.7±3	7.8±3	7.5±2	0.40
E/e' average	10.5±8	10.6±4	9.0±4	0.81
RV assessment				
RA pressure, mm Hg	7.2±3.2	8.6±4.5	9.4±5.5	0.23
Volume overload, n (%)	24 (39)	11 (38)	5 (50)	0.83
PAT, ms	102±30	81±24	86±31	0.01
PAT <100 ms, n (%)	27 (44)	25 (86)	8 (80)	0.0003
RVEDA, cm^2	21.8±5	20.7±5	21.0±6	0.85
RVESA, cm^2	12.4±3	12.0±4	14.1±6	0.45
RVFAC, %	44.4±10	40.7±10	32.8±11	0.08
TAPSE, mm	2.3±0.5	2.3±0.4	2.1±0.7	0.63
RV S', cm/s	11.3±3	11.3±4	10.1±3	0.55
Tei index	0.44±0.26	0.38±0.18	0.44±0.26	0.73

COVID-19 indicates coronavirus disease 2019; EF, ejection fraction; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MEWS, Modified Early Warning Score; PAT, pulmonic acceleration time; RA, right atrium; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; and TAPSE, tricuspid annular plane systolic excursion.

*At the time of baseline echocardiographic evaluation, all patients had dyspnea at rest, stratified to mild disease (oxygen saturation ≥94% at room air; grade 1) in 61, moderate disease (need for noninvasive oxygen; grade 2) in 29, and severe disease (need for mechanical ventilation; grade 3) in 10.

saturation on ambient air (0.92 [HR, 0.86–1.00]; *P*=0.04), higher Sequential Organ Failure Assessment score (1.15 [HR, 1.02–1.33]; *P*=0.03), and higher MEWS (1.16 [HR, 1.05–1.31]; *P*=0.007). The only baseline echocardiographic parameters significantly associated with clinical deterioration were low LVEF (2.9 [HR, 1.1–8.1]; *P*=0.03 for 10% difference) and shorter AT (2.9 [HR, 1.04–8.7]; *P*=0.04 for AT<100 milliseconds; Figure 2A). The only baseline echocardiographic parameters significantly associated with mortality were low LVEF (3.2 [HR, 1.01–8.1]; *P*=0.04 for 10% difference), elevated E/e' ratio (1.08 [HR, 1.01–1.2]; *P*=0.03), increased RV end diastolic area (1.14 [HR, 1.01–1.32]; *P*=0.05 for 1 cm^2), and higher Tei index (1.29 [HR, 1.02–1.7]; *P*=0.03; Figure 2B).

Sequential Echocardiogram During Clinical Deterioration

In 20 patients, sequential echocardiograms were performed because of clinical deterioration (hemodynamic instability, n=2; cardiac deterioration, n=2; respiratory deterioration, n=16). The time to deterioration was 2 to 13 days (median, 3.5 days). The only parameters that changed significantly were RV-related parameters that worsened significantly in patients once they clinically deteriorated. This included shortening of AT (95±20 milliseconds versus 72±17 milliseconds; *P*=0.0002), increase in RV end-diastolic area (20.7±8 cm^2 versus 23.9±4 cm^2; *P*=0.004), and increase in RV end-systolic area (11.9±5 cm^2 versus 14.9±8 cm^2; *P*=0.01, baseline versus follow-up for all). LV-related parameters did not change significantly, with only a trend for decrease in LVEF (57.5±3% versus 55.3±8%) and no consistent change in E/e'. In patients with clinical deterioration, we found several different echocardiographic patterns. Only 5 patients (patients 8, 13, 16, 18, and 19) showed deterioration in LVEF below normal that was associated with an elevation in troponin levels, suggestive of acute LV dysfunction. An example is shown in Movie I in the Data Supplement. The most common echocardiographic pattern (12 of 20, 60%) among deteriorating patients was RV dilatation and dysfunction (combined with LV systolic dysfunction in patients 13 and 18) associated with shortened AT, suggesting elevated pulmonary vascular resistance (in patients 1– 4, 9, 11, 13, 14, 16–18, and 20). In 5 of the latter group (patients 1, 9, 11, 16, and 17), a deep vein thrombus was observed in the femoral or popliteal vein after 5 to 16 days (median, 8 days). An example is shown in Movie II in the Data Supplement. In 7 of them, troponin levels increased from baseline (patients 4, 9, 13, 14, 16, 17, and 20). Of note, there were no significant differences in the levels of D-dimer, CRP, any other laboratory measure, or lung ultrasound score between patients with and those without RV dysfunction (*P*>0.3 for all parameters).The only difference between the patients with RV dysfunction and other deteriorating patients was a higher Sequential Organ Failure Assessment score (3.0 [2–6] versus 1 [1–4]; *P*=0.04). The last 4 patients did not change their LV or RV echocardiographic parameters during clinical deterioration. Examples of patient types are shown in Figures 3 and 4.

DISCUSSION

To the best of our knowledge, this is the first systematic study of all comers with COVID-19 infection requiring hospitalization. Thirty-two percent of patients with COVID-19 infection have normal echocardiography at presentation. To minimize the risk of infection spread, an echocardiogram (or any other imaging test) should be performed only when clinically indicated. In accordance with previous publications of hospitalized patients with

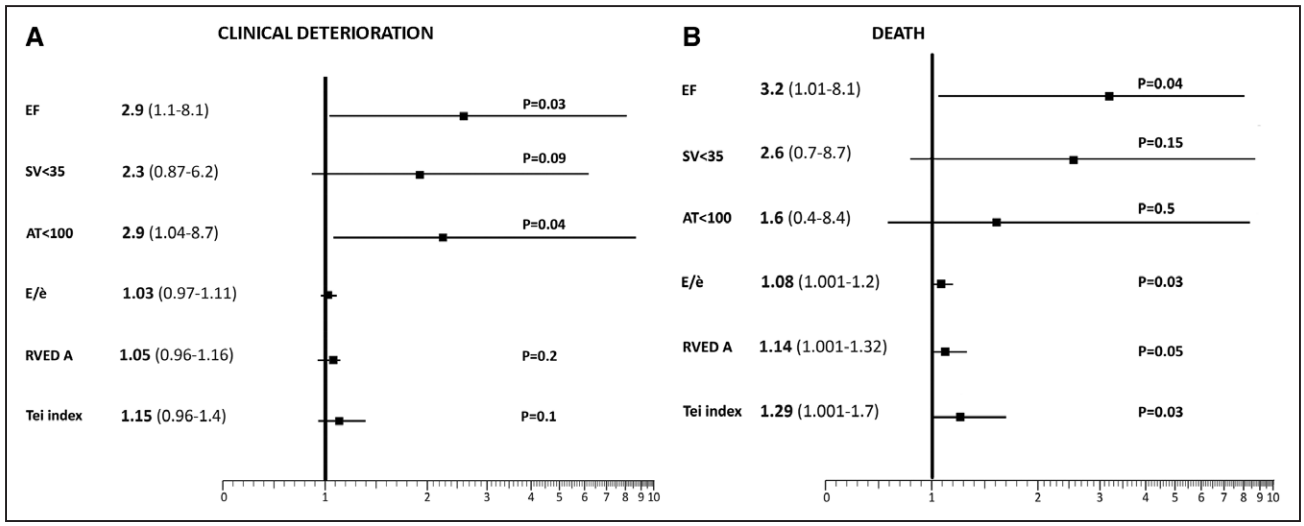

Figure 2. Forest plots for association of imaging with outcome.
A, Forest plot for association of imaging with clinical deterioration. Impact of left and right imaging parameters on clinical deterioration in patients with coronavirus disease 2019 (COVID-19) infection. **B**, Forest plot for association of imaging with mortality. Impact of left and right ventricular imaging parameters on mortality in patients with COVID-19 infection. AT indicates pulmonic acceleration time; EF, ejection fraction; RVEDA, right ventricular end-diastolic area; and SV, stroke volume.

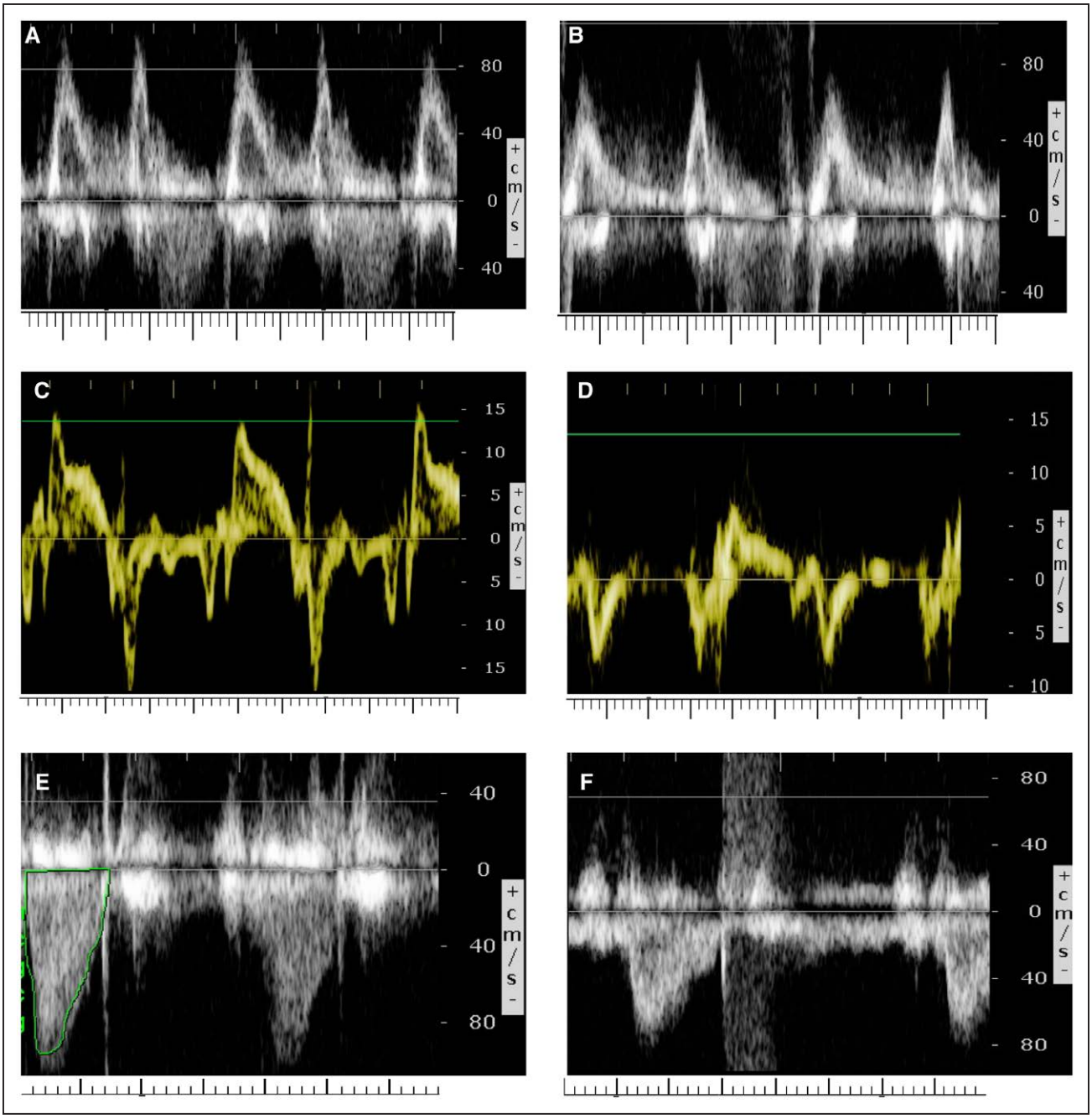

Figure 3. A patient with a sudden decrease in systolic function.
Doppler interrogation of the mitral inflow (**A** and **B**), tissue Doppler of mitral annulus (**C** and **D**), and left ventricular (LV) outflow tract (LVOT) flow (**E** and **F**). Images on the **left** (**A**, **C**, and **E**) are at baseline. Images on the **right** (**B**, **D**, and **F**) were obtained 2 days later, after clinical deterioration and an increase in troponin level. Note the increase in E/e' ratio, suggesting an increase in left filling pressure, and decrease in LV S' and LVOT flow velocity, suggesting a decrease in stroke volume. Time bar scale is 40 milliseconds between every thin line and 200 milliseconds between every thick line.

COVID-19,[1,2] 20% of patients developed clinical deterioration, and in these patients, a second echocardiogram showed further deterioration of the RV parameters, probably related to increased pulmonary resistance. Five of the 12 patients demonstrating RV deterioration had evidence of deep vein thrombosis (DVT) at the femoral veins (also diagnosed by bedside ultrasound).

Although several case reports have raised concern about acute cardiac injury related to the infection or cytokine storm resulting in LV systolic dysfunction in patients with COVID-19 infection,[13,14] we found that the LVEF was only slightly lower in our patients, with 10% of patients showing a reduction of LVEF <50% at the baseline evaluation (including 2 who had documented low LVEF in a previous examination). These results suggest that although LV systolic dysfunction occurs in patients with acute COVID-19 infection, it is not very common. Compared with reference values, patients

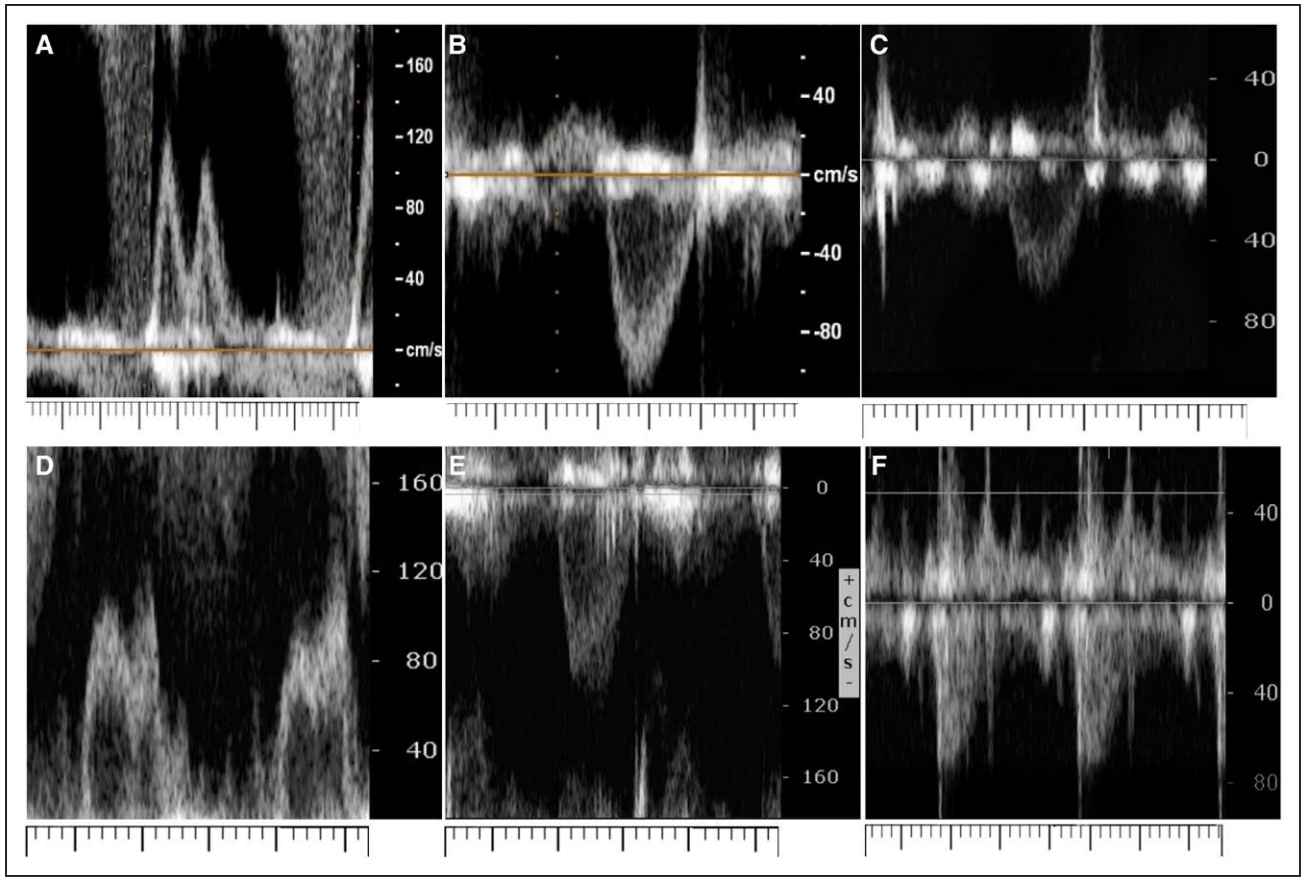

Figure 4. A patient with sudden right ventricular dysfunction with an acute rise in afterload.
Doppler interrogation of mitral inflow (**A** and **D**), left ventricular (LV) outflow tract (LVOT) flow (**B** and **E**), and pulmonary flow acceleration time (**C** and **F**) in patients with right ventricular (RV) dysfunction and deep vein thrombosis. Top images (**A**–**C**) are at baseline; bottom images (**D**–**F**) are after clinical deterioration. Note that mitral inflow velocity decreases as a result of unloading of the LV by the failing RV and the mild decrease in LVOT velocity, suggesting a decrease in stroke volume caused by the underfilled LV. On the **right**, note the change in pulmonic flow acceleration time from symmetrical to early picking, suggesting an elevation in pulmonary vascular resistance. Time bar scale is 40 milliseconds between every thin line and 200 milliseconds between every thick line.

with COVID-19 infection had an increased average E/e′ ratio. However, the majority of patients (80%) did not have clearly elevated LV filling pressure (E/e′≥14).

RV Dysfunction

In contrast to LV parameters, all indexes of RV hemodynamics and function were poorer in patients with COVID-19 infection, especially with elevated troponin, worsening disease grade, or clinical deterioration. The most common abnormal echocardiographic pattern among deteriorating patients (10 of 20, 50%) was RV dilatation and dysfunction associated with shortened AT and normal LV systolic and diastolic function. Many conditions can increase pulmonary vascular resistance or pulmonary pressure in hospitalized patients and precipitate acute RV failure. These conditions include pulmonary embolism (PE) but also hypoxic pulmonary vasoconstriction, decrease in lung volume, excessive positive end-expiratory pressure, pneumonia, hypercarbia, the use of α-agonists, elevated left atrial pressure, or a combination of all these factors. Patients with shorter AT (suggestive of higher pulmonary resistance) were older, had more comorbidities, but, most important, had worse lung disease (based on both chest x-ray and lung ultrasound), lower oxygen saturation, higher LV filling pressure, and higher biomarkers (D-dimer, BNP, troponin-I, and CRP), suggesting that elevated pulmonary vascular resistance in COVID-19 infection is multifactorial and related to parenchymal lung disease, pulmonary vascular disease, and elevated left atrial pressure, all leading to cardiac injury. In 5 of 12 of our patients (42%) with RV dilatation and dysfunction associated with shortened AT, a DVT was observed in the femoral or popliteal vein. We believe that PE is almost certain in these patients. However, because computed tomography angiography increases the risk of disease transmission during transportation from designated COVID-19 areas and inevitably increases the risk of direct contamination of the computed tomography area, we performed computed tomography angiography in only 2 of the remaining 7 patients in whom the expected information seemed to be critical for clinical management. Computed tomography angiography showed clear evidence of PE in one of these patients as well, providing

further support to the notion that PE contributes to worsening of RV function in COVID-19. During acute RV pressure overload, regardless of its cause, RV systolic pressure increases until function begins to decline, resulting in decreased cardiac output and systemic blood pressure, which may result in decrease in coronary perfusion to the RV, troponin leak, and additional reduction in RV contractility. Furthermore, the decrease in the transseptal pressure gradient between the RV and LV may result in septal bowing at the expense of LV volumes, resulting in abnormal orientation of helical myofibrils and a further reduction in cardiac function. This spiral of events may explain, at least in part, the association between echocardiographic parameters of RV dilatation and dysfunction, biomarkers, and early mortality in our cohort.

Troponin Levels and Echocardiography

A recent report suggested that mortality increases with elevation of troponin levels to above the 99th percentile.[3] In that report, the prevalence of heart failure in patients with COVID-19 infection was ≈25%, but this result was based on clinical and laboratory evaluation without cardiac imaging. The 20% prevalence of elevated troponin levels in our cohort was similar to that in previous reports.[3] However, only 3 patients (3 of 20, 15%) had an abnormal LVEF. On the other hand, 6 patients (30%) had E/e'>14 with normal LVEF. From our data, it appears that, in patients with COVID-19 infection, impaired LV diastolic function is more common than LV systolic dysfunction, similar to the results reported for patients with severe acute respiratory syndrome infection[15] or other severe infections.[16] Nevertheless, <50% of patients had either LV systolic or diastolic dysfunction in the elevated troponin COVID-19 cohort. In contrast, RV hemodynamics and function were poorer in patients with COVID-19 infection with elevated troponin, and the most common echocardiographic pattern (10 of 20, 50%) was RV dysfunction associated with shortened AT and normal LV function, suggesting that the most common mechanism for troponin elevation in COVID-19 patients is acute RV dysfunction caused by parenchymal or vascular lung disease.

Lung Ultrasound

Differentiating cardiogenic pulmonary edema from noncardiogenic pulmonary edema resulting from acute respiratory distress syndrome or diffuse viral pneumonia can be challenging. Identification of diffuse B lines, hilar congestion, and bilateral pleural effusions, especially if they are large, can be suggestive of cardiogenic pulmonary edema from left-sided heart failure. On the other side, the presence of subpleural consolidations, pleural line abnormalities such as irregularly thickened or fragmented pleural line, and nonhomogeneous distribution of B lines are more suggestive of noncardiogenic edema. The current definition of acute respiratory distress syndrome requires respiratory failure not explained by cardiac failure or fluid overload and needs objective assessment by echocardiography to exclude hydrostatic edema. In our study, patients underwent lung ultrasound by the same cardiologist performing the echocardiographic recording. E/e' ratio <14 was found in 80% of patients, and hilar congestion (8%) and pleural effusion (16%) were rare, suggesting that the most common reason for the bilateral B-line pattern in patients with COVID-19 infection was related to noncardiogenic pulmonary edema caused by the viral infection, not to elevated LV filling pressures.

Echocardiographic Findings After Clinical Deterioration

In the 20 patients who had repeat, clinically indicated echocardiography, the only parameters that changed significantly were those associated with RV dysfunction. Twenty-five percent showed deterioration in LV systolic function, but the most common echocardiographic pattern was RV dysfunction with or without imaging evidence for peripheral venous thrombosis. Of note, all 5 patients with evidence for DVT developed the identified thrombus despite preventive doses of low-molecular-weight heparin. This finding is in agreement with recent reports suggesting that COVID-19 is associated with high venous thromboembolism rates, elevated D-dimer and fibrinogen levels, and pathological evidence for microvascular lung thrombosis and occlusion.[17] Furthermore, in several small reports, anticoagulant treatment or tissue plasminogen activator treatment was associated with improved outcome in patients with severe COVID-19 infection.[17,18] The high rate of RV dysfunction with or without DVT in our cohort suggests that venous thromboembolism rates or local microvascular lung thrombosis and occlusion may be very common in hospitalized patients with COVID-19 infection, despite routine use of preventive doses of low-molecular-weight heparin. Whether echocardiography-directed use of higher doses of anticoagulation in these patients will reduce the rates of RV dysfunction and improve prognosis needs larger prospective studies.

Study Limitations

Lack of simultaneous electrocardiographic trace limits the evaluation of echocardiographic images, especially those evaluating LV diastolic function and the Tei index of the RV. Our study included only patients with COVID-19 infection who were hospitalized and remained alive and hospitalized for at least 24 hours. The fact that only ≈7% of patients diagnosed with COVID-19 infection in Israel are admitted to the hospital probably led to overestimation of the severity of echocardiographic pathology in COVID-19 infection. Twelve patients (10.7%) were excluded; half of them had "do not resuscitate/intubate" orders, received

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palliative care, and died shortly after their admission. This limitation might create an opposite bias resulting in underestimation of cardiac manifestations in patients with COVID-19 infection. Outcome analyses in our study should be interpreted with caution because of the small number of patients, large CIs, and possible underpower.

Conclusions and Clinical Implications

We describe the first large cohort of echocardiographic studies in patients with COVID-19 infection. One-third of patients had normal echocardiography. Among patients with abnormal echocardiogram at presentation, systolic LV dysfunction was actually uncommon, observed in <10%. The most frequent abnormality was RV dilation with or without dysfunction, possibly related to pulmonary parenchymal or vascular disease. During hospitalization, 20% of patients experienced clinical deterioration, and in these patients, a second echocardiogram showed further deterioration of RV parameters, probably related to increased pulmonary pressures, with or without DVT. Considering the risk of infection spread, we believe that routine echocardiography for all patients with COVID-19 infection is not warranted. On the other hand, an echocardiogram can be crucial in the management of deteriorating patients, allowing better identification of pathogenesis and prompt treatment.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Data Supplement Tables I–V
Data Supplement Movies I and II

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